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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/767,325 | 01/29/2004 | Theodora S. Ross | UM-08737 | 5496 |

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| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/767,325 | ROSS ET AL. | |
| | Examiner | Art Unit | |
| | Brandon J. Fetterolf, PhD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 4-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

### *Response to the Amendment*

The Amendment filed on 03/22/2006 in response to the previous Non-Final Office Action (12/20/2005) is acknowledged and has been entered.

Claims 1 and 4-15 are currently pending.

Claims 12-15 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1 and 4-11 are currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

### *Information Disclosure Statement*

The information disclosure statement filed on 05/10/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

In response to this, Applicants assert that the initial Invention Disclosure Statement was properly submitted, and that Applicants have attached a photocopy of the return receipt postcard, which demonstrates that the USPTO did receive a correctly filed Invention Disclosure Statement. Applicants further submit that a new copy of the IDS is included for the Examiner's Convience.

Regarding Applicants submission of a new IDS and documentation that the initial IDS was received by the USPTO, the Examiner acknowledges that the initial IDS and the new copy have been received by the USPTO and the Examiner. However, the Examiner recognizes that a legible copy of each cited non-patent literature publication has not been received. Specifically, Ford et al. Science 2001; 291: 1051. As such, as indicated by the previous signed IDS, the Ford et al. reference has not been considered.

**Rejections Maintained:**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3-11 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between he steps. See MPEP § 2172.01. The omitted steps are: a correlation step describing how the results of the method relate back to the preamble of the method objectives.

In response to this rejection, Applicants contend that claims 1 has been amended to include additional language that relates the method back to the method preamble.

This argument has been carefully considered, but is not found persuasive.

Regarding Applicants contention that claim 1 has been amended to include additional language that relates the method back to the method preamble, the Examiner acknowledges that the claims have been amended to recite "wherein the presence of antibodies to HIP in said sample is indicative of prostate cancer in said subject". However, the Examiner recognizes that there does not appear to be a reference, i.e. control, antibodies to HIP1 antibodies are compared to. As such, it is unclear whether the presence of antibodies to HIP1 are indicative of cancer or an increase in antibodies to HIP1 as compared to the control is indicative of cancer.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine

screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method for detecting cancer, comprising providing a sample from a subject suspected of having cancer and detecting the presence or absence of antibodies to HIP1, wherein the presence of antibodies to HIP1 is indicative of cancer. Thus, the claims imply that the presence or absence of antibodies to HIP1 in any sample can be used to detect any and/or all cancers.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to detecting any and/or all cancers comprising providing a sample from a subject suspected of having cancer; and detecting the presence or absence of antibodies to HIP1 in said sample, wherein the presence of antibodies to HIP1 is indicative of cancer. The specification teaches (page 36, lines 1-10) that experiments conducted during the course of development of the present invention have demonstrated that subjects with prostate cancer preferentially exhibit a humoral response to HIP1. For example, the specification provides (page 83, lines 10-14) a humoral response to HIP1 in a TRAMP mouse model for prostate cancer, wherein 10/20 Tag positive TRAMP mice had antibodies in their serum to HIP1 whereas 0/10 normal Tag negative mice had antibodies in their serum to HIP1. In addition to the TRAMP mouse model, the specification teaches (page 82, Example 8) a humoral response to HIP1 in human prostate cancer patients, wherein 5/20 were positive for a humoral response to HIP1 in the prostate cancer patient cohort whereas 9/23 were positive in the "normal" patient cohort. Thus, while the specification appears to imply a nexus

between a correlation between cancer detection and autoantibody presence to HIP1 in the TRAMP mouse model, the specification does not appear to clearly indicate whether or not antibodies to HIP1 is indicative of the cancerous state in a cancer patient. In other words, what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as detecting the presence or absence of cancer. In the instant case, the TRAMP mouse model is an art recognized transgenic model of prostate cancer, which recapitulates many of the features of prostate cancer in humans (*see* Gupta, S. International Journal of Oncology 2004; 25: 1133-1148). For example, Gupta discusses that the TRAMP model has been used for a wide range of studies including the analysis of growth factors, assessment of intermediate and endpoint markers, markers of angiogenesis, and for evaluating the efficacy of natural agents and synthetic compounds in chemoprevention and therapy of prostate cancer (page 1138, 2nd column, beginning on the bottom to page 1140, 1st column). Thus, while the prior art teaches that the TRAMP mouse model is useful for a variety of studies, the art is silent with regards to the production of a humoral response to a specific cancer related antigen and using these results as a diagnostic marker for cancer. Furthermore, if a molecule such as an antibody to HIP1 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some type of pattern that would allow the claimed antibody to be used in a diagnostic manner. For example, antibodies to HIP1 were found in serum of "normal" patients, as well as patients suffering from prostate cancer as evidenced by the disclosure (page 82, Example 2). Similarly, the specification teaches (page 63, lines 1+) that many proteins such as HIP1 are expressed in normal tissues and diseased tissues. Therefore, one needs to know that antibodies to HIP1 are present only in a cancer patient to the exclusion of normal patients. Thus, in the absence of any correlation between antibodies to HIP1 with any known disease or disorder, any information obtained from various profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself. Therefore, absent evidence of the antibodies to HIP1 presence including the correlation to a diseased state, one of skill in the art would not be able to predictably use antibodies to HIP1 in any diagnostic setting without undue experimentation.

Reasonable correlation must exist between the scope of the claims and the scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working

examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

In response to this rejection, Applicants assert that claim 1 has been amended to specify that the presence of HIP1 antibodies is indicative of prostate cancer in the subject. Applicants further submit that Figure 28 clearly indicates that a greater number of the prostate cancer samples were positive for antibodies to HIP1 than normal prostate controls. In addition, Applicants contend that Example 8 states "This give the screening test a significance of $P<0.025$ (chi squared) and a 75% sensitivity and 61% specificity." (page 83, lines 5-6). As such, Applicants submit that they have demonstrated a correlation between serum antibodies to HIP1 and prostate cancer.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that claim 1 has been amended to recite that the presence of antibodies to HIP1 is said sample is indicative of prostate cancer, and further, that the Figure 28 and Example 8 (page 83, lines 5-6) of the specification disclose antibodies to HIP1 being present in a greater number of prostate samples than normal controls, the Examiner acknowledges that Figure 28 appears to depict antibodies to HIP1 being present in a greater number of prostate cancer samples than normal controls. However, the Examiner recognizes that Example 8 (page 83, lines 4-5) discloses "5/20 were positive for a humoral response to HIP1 in the prostate cancer patient cohort and 9/23 were positive in the "normal" patient cohort." In other words, 25% of the prostate cancer patient cohort was positive for a humoral response to HIP1, whereas 39% of the "normal" patient cohort were positive. In view of this teaching, it appears that the presence of antibodies to HIP1, e.g., positive humoral response to HIP1, would be more indicative of a "normal" patient and not of a patient suffering from prostate cancer. Lastly, assuming *arguendo*, that the presence of antibodies to HIP1 in serum samples is indicative of prostate cancer as argued by Applicants (remarks, page 5), the specification does not reasonably provide enablement for a method of detecting cancer comprising providing any and/or all samples from a subject suspected of having cancer; and detecting the presence or absence of antibodies to HIP1, in said sample, wherein the presence of antibodies to HIP1 in said sample is indicative of prostate cancer. For example, the specification does not appear to reasonably convey the presence or absence of antibodies to HIP1 in any sample other than a serum sample. In the instant case, if the sample was urine, those of skill in the art would recognize the unpredictability of detecting antibodies to a

particular cancer antigen in urine. For example, a search of the prior art only appeared to reveal the detection of one particular type of cancer (muliple myleoma) by detecting a particular light chain antibody in the urine. Specifically, Murphy *et al.* (Murphy, G.P., Lawrence, W., and Lenhard, R.E. 1995. Clinical Oncology. 2nd edition. Atlanta, GA: American Cancer Society. 470-485) disclose that dense tubular casts are a hallmark of MM (*multiple myeloma*) and are observed in 75% of patients, all of whom are excreting free light chains, or Bence-Jones proteins (page 479, 2nd column, 2nd paragraph). Additionally, those of skill in the art would recognize the unpredictability of identifying any autoantibody present in urine, which are characteristic of cancer. Levine (Levine, R. 1990. Pharmacology: Drug Actions and Reactions. 4th edition. Boston, Mass: Little ,Brown & Co, 140-141.) teaches the difficulty of renal excretion of drugs. Specifically, Levine (page 140 to 141) discloses that any drug that is free in the plasma will be filtered together with other plasma constituents and that only drugs bound to protein or drugs of excessively large molecular size will be retained in the bloodstream. It is well known in the art that antibodies are high molecular weight proteins (<http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=antibody>). Thus, those of ordinary skill in the art would predict that such proteins are more often than not sequestered in the serum, rather than the urine. Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification that any/and all disorders can be determined by detecting an antibody in the urine that is characteristic of the disorder.

Therefore, NO claim is allowed

**All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.**

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER